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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/410,319	Titievsky et al.
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- *If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.*
- *If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.*
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).*
- *Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).*

Status

1) ☒ *Responsive to communication(s) filed on Apr 30, 2001 .*

2a) ☐ *This action is* **FINAL.** 2b) ☒ *This action is non-final.*

3) ☐ *Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.*

Disposition of Claims

4) ☒ *Claim(s) 1-91 is/are pending in the application.*

4a) *Of the above, claim(s) _____ is/are withdrawn from consideration.*

5) ☐ *Claim(s) _____ is/are allowed.*

6) ☒ *Claim(s) 1-91 is/are rejected.*

7) ☐ *Claim(s) _____ is/are objected to.*

8) ☐ *Claims _____ are subject to restriction and/or election requirement.*

Application Papers

9) ☐ *The specification is objected to by the Examiner.*

10) ☐ *The drawing(s) filed on _____ is/are objected to by the Examiner.*

11) ☐ *The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.*

12) ☐ *The oath or declaration is objected to by the Examiner.*

Priority under 35 U.S.C. § 119

13) ☐ *Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).*

a) ☐ *All* b) ☐ *Some** c) ☐ *None of:*

1. ☐ *Certified copies of the priority documents have been received.*
2. ☐ *Certified copies of the priority documents have been received in Application No. _____ .*
3. ☐ *Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).*

**See the attached detailed Office action for a list of the certified copies not received.*

14) ☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

Attachment(s)

15) ☒ *Notice of References Cited (PTO-892)*

16) ☐ *Notice of Draftsperson's Patent Drawing Review (PTO-948)*

17) ☒ *Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6*

18) ☐ *Interview Summary (PTO-413) Paper No(s). _____*

19) ☐ *Notice of Informal Patent Application (PTO-152)*

20) ☐ *Other:*

DETAILED ACTION

Specification

1. Applicant has elected claims of Group I without traverse corresponding to claims 1-91 for further prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 1, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an agonist of intracellular signaling effect while the final process step is that of determining whether intracellular signaling has been effected in step (ii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather determining whether intracellular signaling has been effected in step (ii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method

which were stated in the method's preamble. Claim 1 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 16 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 16, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an antagonist of intracellular signaling effect while the final process step is that of comparing the results to controls not incubated with the compound in step (iii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather comparing the results to controls not incubated with the compound in step (iii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 16 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 30 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 30, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an agonist of intracellular signaling effect while the final process step is that of determining whether intracellular signaling has been effected in step (ii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather determining whether intracellular signaling has been effected in step (ii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method

which were stated in the method's preamble. Claim 30 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 39 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 39, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an antagonist of intracellular signaling effect while the final process step is that of comparing the results to controls not incubated with the compound in step (iii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather comparing the results to controls not incubated with the compound in step (iii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 39 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 49 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 49, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an agonist of intracellular signaling effect while the final process step is that of determining whether an increase in intracellular Calcium concentration is effected in the cells as compared to controls not incubated with the compound in step (iii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather determining whether an increase in intracellular Calcium concentration is effected in the cells as compared to

controls not incubated with the compound in step (iii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 49 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 54 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 54, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an antagonist of intracellular signaling effect while the final process step is that of determining whether a decrease in intracellular Calcium concentration is effected in the cells as compared to controls not incubated with the compound in step (iii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather determining whether a decrease in intracellular Calcium concentration is effected in the cells as compared to controls not incubated with the compound in step (iii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 54 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 59 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 59, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an agonist of intracellular signaling effect while the final process step is that of performing an assay

for measuring kinase phosphorylation on the immunoprecipitate in step (iv) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather performing an assay for measuring kinase phosphorylation on the immunoprecipitate in step (iv). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 59 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 63 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 63, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an antagonist of intracellular signaling effect while the final process step is that of comparing the results of the assay to those achieved in control experiments performed in the absence of the compound to be tested in step (v) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather comparing the results of the assay to those achieved in control experiments performed in the absence of the compound to be tested in step (v). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 63 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 68 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 68, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an agonist of intracellular signaling effect while the final process step is that of determining whether activation of Src-type kinase is effected, as compared with controls, not incubated with the compound in step (ii) and it is thus unclear as to whether the instantly claimed method is drawn to a method for identifying a compound or rather determining whether activation of Src-type kinase is effected, as compared with controls, not incubated with the compound in step (ii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 68 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 75 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 75, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an antagonist of intracellular signaling effect while the final process step is that of determining whether deactivation of Src-type kinase is effected, as compared with controls, not incubated with the compound in step (ii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for determining whether deactivation of Src-type kinase is effected, as compared with controls, not incubated with the compound in step (ii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method

which were stated in the method's preamble. Claim 75 lacks such a last step and are confusing because the additional method step is not sufficiently set forth.

Claim 83 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 83, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an agonist of intracellular signaling effect while the final process step is that of determining whether activation of Src-type kinase is effected, as compared with controls, not incubated with the compound in step (ii) and it is thus unclear as to whether the instantly claimed methods are drawn to a method for identifying a compound or rather determining whether activation of Src-type kinase is effected, as compared with controls, not incubated with the compound in step (ii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 83 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

Claim 87 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 87, the preamble of the instantly claimed method is drawn to a method for identifying a compound that is an antagonist of intracellular signaling effect while the final process step is that of comparing the results of the assay to those achieved in control experiments performed in the absence of the compound to be tested in step (ii) and it is thus unclear as to whether the instantly claimed method is drawn to a method for identifying a compound or rather comparing the results of the

assay to those achieved in control experiments performed in the absence of the compound to be tested in step (ii). Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 87 lacks such a last step and is confusing because the additional method step is not sufficiently set forth.

While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that amended claims more clearly describing the intended steps be submitted.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

5. Claims 1 and 16 are rejected under 35 U.S.C. 102 (e) as being anticipated by Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999).

Jefferies et al teach a method for identifying a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells comprising

(I) incubating the nervous system cells having GPI-anchored receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells (Column 8, lines 30-48 and Column 25, lines 38-58 and Figure 1). This rejection is based on the fact that iron uptake in the cell inherently causes intracellular signaling (See also Column 7).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-6, 16- 21, 30, 32, 39, 40 and 42 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997) in view of

Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Cacalano et al. (Neuron, (1998), Vol. 21, pages 53-62).

Ibanez et al teach a method for identifying GDNF analogs that is an agonist of intracellular signaling effected by c-RET receptors in nervous system cells comprising (I) incubating the nervous system cells having c-RET receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells (Claims 10, 16 and 18).

Ibanez et al teach a method wherein the nervous system cells are neuroblastoma cells (Claims 11, 17 and 19).

Ibanez et al do not teach a method for identifying an antagonist of intracellular signaling effected by c-RET receptors in nervous system cells comprising (I) incubating the nervous system cells having c-RET receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells.

Jefferies et al teach a method for identifying a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells comprising (I) incubating the nervous system cells having GPI-anchored receptors with a test compound and (ii) determining whether intracellular signaling has been effected in the cells (Column 8, lines 30-48 and Column 25, lines 38-58).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the antagonist of intracellular signaling detection of Jefferies et al. in the method of identifying compounds of Ibanez et al., since

Jefferies et al. state, "Accordingly, substances may be identified which are effective in the treatment of Alzheimer's disease (Column 10, lines 56-58)." An ordinary practitioner would have been motivated to combine and substitute the antagonist of intracellular signalling detection of Jefferies et al. in the method of identifying compounds of Ibanez et al., in order to achieve the express advantages noted by Jefferies et al of an invention which supports the identification of substances effective in the treatment of Alzheimer's disease.

Ibanez et al in view of Jefferies et al. do not teach a method wherein GDNF is linked to GPI-anchored proteins.

Cacalano et al. teach a method wherein GDNF is linked to GPI-anchored proteins (Abstract).

Ibanez et al in view of Jefferies et al. do not teach a method wherein the nervous system cells express GFRalpha1 receptors but not Ret receptors.

Cacalano et al. teach a method wherein the nervous system cells express GFRalpha1 receptors but not Ret receptors. (Discussion Section).

Ibanez et al in view of Jefferies et al. do not teach a method wherein the nervous system cells are DRG neurons Ret (-/-).

Cacalano et al. teach a method wherein the nervous system cells are DRG neurons Ret (-/-). (Discussion Section).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the GDNF- linked to GPI-anchored proteins

GFRalpha1 receptors of Cacalano et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al., since Cacalano et al. state, "In summary, the striking similarities between the GFRalpha1 (-/-), GDNF (-/-), and Ret (-/-) mice support the hypothesis that GFRalpha1 is an important receptor component for GDNF and validate the physiological significance of GFRalpha and the multicomponent receptor hypothesis (Page 60, column 1, second paragraph, lines 1-5)." An ordinary practitioner would have been motivated to combine and substitute the GDNF- linked to GPI-anchored proteins GFRalpha1 receptors of Cacalano et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al., in order to achieve the express advantages noted by Cacalano et al of an invention which supports the hypothesis that GFRalpha1 is an important receptor component for GDNF and validate the physiological significance of GFRalpha.

8. Claims 1-10, 15- 24, 29-33, 38-40, 42 , 43 and 48-58 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997)in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Cacalano et al. (Neuron, (1998), Vol. 21, pages 53-62) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023).

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al teach methods of claims 1-6, 16- 21, 30, 32, 39, 40 and 42 as described above.

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al do not teach the method wherein the intracellular signaling is measured as an increase in intracellular Calcium concentration as compared to controls not incubated with the compound.

Shen et al teach the method wherein the intracellular signaling is measured as an increase in intracellular Calcium concentration as compared to controls not incubated with the compound. (Abstract and Figure 4 and Materials and Methods Section, Ca 2+ flux assay subsection).

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al do not teach the method wherein the intracellular signaling is measured as kinase activation by (I) preparing a cell lysate, (ii) immunoprecipitating the cell lysate with an anti GPI-anchored antibody to form an immunoprecipitate, (iii) performing an assay to measure kinase phosphorylation on the immunoprecipitate, and (iv) comparing the results with controls not incubated with the compound.

Shen et al teach the method wherein the intracellular signaling is measured as kinase activation by (I) preparing a cell lysate, (ii) immunoprecipitating the cell lysate with an anti GPI-anchored antibody to form an immunoprecipitate, (iii) performing an assay to measure kinase phosphorylation on the immunoprecipitate, and (iv) comparing the results with controls not incubated with the compound. (Abstract, Materials and Methods Section, Immunoprecipitation subsection and Figures 1-3).

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al do not teach the method wherein the kinase is measured as PLCgamma activation.

Shen et al teach the method wherein the kinase is measured as PLCgamma activation. (Abstract and Figures 3 and 5)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the intracellular signaling measurement by an increase in intracellular Calcium concentration and PLCgamma activation and immunoprecipitation of Shen et al. in the method of identifying compounds of Ibanez et al. in view of Cacalano et al , since Shen et al. state, "Activation of protein tyrosine kinase after ligand binding has been shown to be the primary event for signaling by members of the multichain immune recognition receptor family (Page 3022, column 1, lines 8-11)." An ordinary practitioner would have been motivated to combine and substitute the intracellular signaling measurement by an increase in intracellular Calcium concentration and PLCgamma activation and immunoprecipitation of Shen et al. in the method of identifying compounds of Ibanez et al. in view of Cacalano et al, in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the express advantages noted by Shen et al., of a biochemical pathway i.e., activation of protein tyrosine kinase after ligand binding that has been shown to be the primary event for signaling by members of the multichain immune recognition receptor family.

9. Claims 1-10, 12- 13, 15-24, 26-27, 29-33, 35-36, 38-40, 42 , 43, 45-46, 48-58 , 68, 69, 70, 75, 76, 77, 79-82, 83-85, 87-89 and 91 are rejected under 35 U.S.C. 103 (a) over Ibanez et al.

(PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Cacalano et al. (Neuron, (1998), Vol. 21, pages 53-62) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023) further in view of Dikic et al. (Nature, (1996), Vol. 383, pages 547-549).

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. teach methods of claims 1-10, 15- 24, 29-33, 38-40, 42 , 43 and 48-58 as described above.

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al do not teach the method wherein the kinase is Src-type kinase that is measured by activation of MAPK.

Dikic et al. teach the method wherein the kinase is Src-type kinase that is measured by activation of MAPK. (Abstract, Figure 4 and Methods Section, Kinase Assays subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Src-type kinase that is measured by activation of MAPK of Dikic et al. in the method of identifying compounds of Ibanez et al.in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al., since Dikic et al. state, "Src family protein tyrosine kinases, which are expressed in every cell type and tissue, appear to be a common and important component of this pathway, acting together with cell-type-specific protein tyrosine kinases, such as Pyk2 in PC12 cells or Syk in avian B cells, to bring about a cell-type-specific signal for linking G-protein coupled receptors with the MAP kinase

signaling pathway and hence the transcriptional machinery (Page 549, Column 2, last sentence)." An ordinary practitioner would have been motivated to combine and substitute the Src-type kinase that is measured by activation of MAPK of Dikic et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al., in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the express advantages , as noted by of Dikic et al , of the Src family protein tyrosine kinases, which are expressed in every cell type and tissue, appear to be a common and important component of this pathway, acting together with cell-type-specific protein tyrosine kinases to bring about a cell-type-specific signal for linking G-protein coupled receptors with the MAP kinase signaling pathway and hence the transcriptional machinery.

10. Claims 1-10, 12-24, 26-33, 35-40, 42 , 43, 45-58 , 68, 69, 70, 71, 75, 76, 77-82, 83-89 and 90-91 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Cacalano et al. (Neuron, (1998), Vol. 21, pages 53-62) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023) further in view of Dikic et al. (Nature, (1996), Vol. 383, pages 547-549) further in view of Finkbeiner et al. (Neuron, (1997), Vol. 19, pages 1031-1047).

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. further in view of Dikic et al teach methods of claims 1-10, 12- 13, 15-24, 26-27, 29-

33, 35-36, 38-40, 42 , 43, 45-46, 48-58 , 68, 69, 70, 75, 76, 77, 79-82, 83-85, 87-89 and 91 described above.

Ibanez et al. in view of Cacalano et al in view of Jefferies et al. further in view of Shen et al further in view of Dikic et al do not teach the method wherein the activation of Src-type kinase is measured as activation of CREB.

Finkbeiner et al. teach the method wherein the activation of Src-type kinase is measured as activation of CREB(Abstract and Figures 2, 10 and 12).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the activation of Src-type kinase that is measured as activation of CREB of Finkbeiner et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. further in view of Dikic et al, since Finkbeiner et al. state, "These findings reveal a previously unrecognized, CaMK-dependent mechanism by which neutrophins activate CREB and suggest that CREB plays a central role in mediating neutrophin responses in neurons (Abstract, last sentence)." An ordinary practitioner would have been motivated to combine and substitute the activation of Src-type kinase that is measured as activation of CREB of Finkbeiner et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. further in view of Dikic et al, in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the

express advantages, as noted by Finkbeiner et al., of CREB that plays a central role in mediating neutrophin responses in neurons.

11. Claims 1-91 are rejected under 35 U.S.C. 103 (a) over Ibanez et al. (PCT International Application Number WO 97/18240) (May 22, 1997) in view of Jefferies et al. (U.S. Patent 5,981,194) (November 9, 1999) further in view of Cacalano et al. (Neuron, (1998), Vol. 21, pages 53-62) further in view of Shen et al. (Journal of Immunology, (1994), Vol. 152, pages 3017-3023) further in view of Dikic et al. (Nature, (1996), Vol. 383, pages 547-549) further in view of Finkbeiner et al. (Neuron, (1997), Vol. 19, pages 1031-1047) further in view of Chalazonitis et al. (Developmental Biology, (1998), Vol. 204, pages 385-406).

Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. further in view of Dikic et al further in view of Finkbeiner et al. teach methods of claims 1-10, 12-24, 26-33, 35-40, 42 , 43, 45-58 , 68, 69, 70, 71, 75, 76, 77-82, and 83-91 as described above.

Ibanez et al.in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al further in view of Dikic et al further in view of Finkbeiner et al. do not teach the method wherein the antibody is anti-GFRalpha1.

Chalazonitis et al teach the method wherein the antibody is anti-GFRalpha1 (Figures 12, 15 and Materials and Methods Section, Immunocytochemistry Subsection).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the antibody assay using anti-GFRalpha1 of

Chalazonitis et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. further in view of Dikic et al further in view of Finkbeiner et al., since Chalazonitis et al. state, "The number of GFRalpha-1 immunoreactive cells in cultures was found in the current study to be greatly increased by exposure to GDNF, an effect that could be explained by an ability of GDNF to enhance the expression of its own receptor. Alternatively, the GDNF-induced increase in GFRalpha-1 immunoreactive cells may simply reflect the enhanced development in the presence of GDNF of neurons, which are the cells that anchor GFRalpha-1 (Page 401, column 1, last paragraph to column 2, line 8)." An ordinary practitioner would have been motivated to combine and substitute the antibody assay using anti-GFRalpha1 of Chalazonitis et al. in the method of identifying compounds of Ibanez et al. in view of Jefferies et al. further in view of Cacalano et al further in view of Shen et al. further in view of Dikic et al further in view of Finkbeiner et al., in order to improve the identification method of a compound that is an agonist or antagonist of intracellular signaling effected by GPI-anchored receptors in nervous system cells and also in order to achieve the express advantages, as noted by Chalazonitis et al., of an antibody that can detect the ability of GDNF to enhance the expression of its own receptor.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152.

Any inquiry of general nature or relating to the status of this application should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Kr. Chakrabarti

Arun Chakrabarti,

Patent Examiner

Art Unit 1655

May 9, 2001

JEFFREY FRED
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